UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte THOMAS W. LEONARD

Appeal No. 2005-1874
Application No. 10/041,916

ON BRIEF

Before WILLIAM F. SMITH, MILLS, and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-19, which are all of the claims pending in this application.

The claims 1, 9 and 15 are representative of the claims before us and are set forth below:

1. A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of:
a) reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens, wherein the estrogens are selected from the group consisting of $\Delta^{8,9}$-dehydroestrone, estrone, equilin, 17α-estradiol, 17β-estradiol, 17α-dihydroequilin, 17β-dihydroequilin, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, 17α-$\Delta^{8,9}$-dehydroestradiol, 17β-$\Delta^{8,9}$-dehydroestradiol, 6-OH equilenin, 6-O-17α-dihydroequilenin, 6-OH- 17β-dihydroequilenin, ethinyl estradiol and estradiol valerate;

b) adding a stabilizing amount of tris(hydroxymethyl)aminomethane; and
c) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane.

9. The process according to claim 1 further comprising the step of obtaining the mixture of alkali metal salts of estrogens by reacting a mixture of estrogens with an alkali metal hydride in apolar, aprotic solvent.

15. A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of:

a) reacting a mixture of at least two estrogens with sodium hydroxide in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens;

b) reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in apolar, aprotic solvent to provide a mixture of sulfated metal salts of estrogens;

c) adding a stabilizing agent of tris(hydroxymethyl)aminomethane; and

d) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane.

The prior art references relied upon by the examiner are:

Simoons et al. (Simoons)	4,154,820	May 15, 1979
Raveendranath et al. (Raveendranath)	5,288,717	Feb. 22, 1994
Bender et al. (Bender)	5,998,638	Dec. 7, 1999
Raijmakers et al. (Raijmakers)	5,998,639	Dec. 7, 1999
Kong et al. (Kong)	6,458,778	Oct. 1, 2002
Shah et al. (Shah)	6,525,039	Feb. 25, 2003

Grounds of Rejection

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as obvious over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination.

We affirm this rejection.

Claim Grouping

According to appellant, claims 1-8 stand or fall together, claims 9-14 stand or fall together and claims 15-19 stand or fall together. Brief, page 3. Thus we select claims 1, 9 and 15 as representative of the claims before us. 37 C.F.R. § 1.192(c)(7)(2004), superseded by 37 C.F.R. § 41.37(c)(1)(vii) (September 13, 2004).

DISCUSSION

35 U.S.C. § 103(a)

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as obvious over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). It is well-established that the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

It is the examiner's position that (Answer, page 4):

> Raijmakers [] teach sulfatation of estrogen mixtures (see entire article, especially Examples 12-14).
>
> Simoons teaches a stabilized composition of estrogens utilizing Tris (see Examples 1-V, especially col. 7, lines 27-40).
>
> Raveendranath [] teach a process for the production of alkali metal 8,9-dehydroestrone sulfate esters and the production of stabilized composition with Tris.... The reference teaches [a] mixture of 8,9-dehydroestrone with sodium hydride, reaction with trimethylamine-sulfur trioxide and addition of Tris (see Examples 1-7).
>
> Each of Shah [], Bender [], and Kong [] teach the production of sulfate esters of estrogens by reaction with a sulfur trioxide complex, such as trimethylamine sulfur trioxide or triethylamine-sulfur trioxide. Shah also teaches the production of sulfate ester of an estrogen by first mixing said compound with sodium hydride before reacting with sulfur trioxide (see Example 1, method A).

The examiner concludes that (Answer, pages 4-5):

> [t]he sulfatation of estrogen mixture would have been obvious to the skilled artisan at the time of the invention because (a) sulfatation of alcohols such as sterols utilizing sulfur trioxide complex is well known in the art as evident by Raveendranath, Shah, Bender and Kong; (b) addition of a stabilizer such as Tris to estrogenic compositions is also well known in the art as evident by Simoons and Raveendranath and (c) the level of skill of the ordinary artisan in the art at the time of the invention. ....The motivation to make a stabilized composition comprising sulfated estrogens is based on the knowledge in the art that compositions comprising a mixture of estrogenic sulfate esters are useful in hormone replacement therapy (see for example, '820 [Simoons], col. 1, lines 20-31).

We agree that the examiner has a established a prima facie case of obviousness in view of the cited references. In particular, Raveendranath appears to teach every step of the claimed process except it teaches reacting a sulfur trioxide complex with a single alkali metal salt of an estrogen instead of the claimed mixture of

alkali metal salts of estrogens. The examiner relies on Simoons for its disclosure of the stability of mixtures of alkali metal salts of estrogens and their use in combination with tris.[1] Col. 4, lines 32-43 and Col. 7, lines 15-40, Example 1. The remaining references, Shah, Bender and Kong describe the production of sulfate esters of estrogens by reaction with a sulfur trioxide complex, such as trimethylamine sulfur trioxide or triethylamine-sulfur trioxide. Therefore we agree with the examiner that it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to expect that stable mixtures of alkali metal salts of estrogens could also be obtained by the process of Raveendranath.

Where the prior art, as here, gives reason or motivation to make the claimed invention, the burden then falls on an appellants to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is pertinent. In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

In rebuttal, appellant argues that "[n]one of the references teach or suggest a process for producing a mixture of sulfated estrogens wherein the process involves reacting a mixture of at least two alkali metal salts of estrogens to provide for a mixture of alkali metal salts of estrogens." [Emphasis original.] Brief, page 7.

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[1] Tris is an abbreviation for tris(hydroxymethyl)aminomethane.

Appellant, however, would appear to acknowledge that Raveendranath teaches the exact same process except for the reaction of a mixture of estrogens. Brief, page 9; Specification, pages 1-2. Appellant argues that Simoons and Raijmakers do not motivate the formation of a mixture of sulfated estrogens if combined with Raveendranath. Brief, page 10. First, appellant argues that the composition mixtures of Simoons do not include alkali metal salts of 8,9-dehydroestrone sulfate esters. For this reason, appellant concludes that one of ordinary skill in the art would not combine the product of Raveendranath in a composition mixture of Simoons because Simoons does not propose that 8,9-dehydroestrones are desired in such a mixture. Id. We are not persuaded by this argument.

Simoons discusses generally the instability of estrogens, Col. 1, line 44 to Col. 2, lines 6, and suggests that the stability of alkali metal salts of estrogens can be improved, Col. 4, lines 32-43, especially in the presence of Tris, Col. 9, lines 14-28. Simoons states that mixtures of estrogens can be stabilized using tris. Col. 4, line 37; Col. 7, lines 26-40. In our view it is of no consequence that the one particular estrogen argued by appellant and set forth in the Markush group of estrogens in claim 1 is not recited in Simoons when other estrogen compound mixtures within the scope of claim 1 are recited in Simoons.

Second, Appellant argues that the processes of Raveendranath and Raijmakers are not compatible because "the process of Raijmakers et al is 'ineffective in the sulfation of 8,9-dehydroestrone.'" Brief, page 11. However, the examiner relies on

Raveendranath for disclosure of the claimed process, not Raijmakers, and any deficiencies in the process of Raijmakers related to sulfation of 8,9-dehydrostrone have been overcome by the process of Raveendranath.

Furthermore, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). The test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). For the reasons discussed in detail above, we conclude that the combined teachings of the cited references would have rendered the claimed invention prima facie obvious.

In view of the above, Appellant has failed to rebut the prima facie case of obviousness established by the examiner with sufficient argument or evidence and the rejection of claims 1-8 under 35 U.S.C. § 103(a) as obvious over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination is affirmed.

Claim 9

Claim 9 is the same process as claim 1, but further comprises a step of obtaining the mixture of alkali metal salts of estrogens by reacting a mixture of estrogens with an alkali metal hydride in a polar, aprotic solvent.

The examiner notes that Raveendranath describes, '[t]he initial production of an alkali metal salt of 8,9-dehydroestrone followed by sulfation with trimethylaminesulfur-trioxide under mild conditions in a polar, aprotic solvent such a tetrahydrofuran with simultaneous or subsequent addition of tris(hydroxymethyl)-aminomethane as a stabilizer." Col. 1, lines 53-59. See also Answer, pages 6-7.

According to the examiner the "difference between the claimed invention and that of Raveendranath lies in the recitation of a starting material containing at least two estrogens or alkali metal salts thereof." Answer, page 7. Appellant also acknowledges this difference, arguing, the "combination of references fails to teach or suggest the formation of a mixture of alkali metal salts of estrogens..." Brief, pages 11-12.

As indicated above, in our view the combination of Raveendranath and Simoons addresses this difference. The combination of references also describes the use of a polar, aprotic solvent, as claimed. Thus, the rejection of claims 9-14 over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination, is affirmed.

Claim 15

Claim 15 recites a process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of:

a) reacting a mixture of at least two estrogens with sodium hydroxide in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens;

b) reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in an apolar, aprotic solvent to provide a mixture of sulfated metal salts of estrogens;

c) adding a stabilizing agent of tris(hydroxymethyl)aminomethane; and

d) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane.

Claim 15 differs from claim 1 in that it recites a step b) "reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in apolar, aprotic solvent to provide a mixture of sulfated metal salts of estrogens".

As indicated above with respect to the rejection of claim 9, Raveendranath describes, '[t]he initial production of an alkali metal salt of 8,9-dehydroestrone followed by sulfation with trimethylaminesulfurtrioxide under mild conditions in apolar, aprotic solvent such a tetrahydrofuran with simultaneous or subsequent addition of tris(hydroxymethyl)-aminomethane as a stabilizer." Col. 1, lines 53-59. See also Answer, pages 6-7. All other claim 15 steps were substantially present in claim 1 and are addressed in the discussion with respect to claim 1, above.

In view of the above, the rejection of claims 15-19 over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination, is affirmed.

CONCLUSION

The rejection of claims 1-19 under 35 U.S.C. § 103(a) as obvious over Raijmakers, Simoons, Raveendranath, Shah, Bender and Kong in combination is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

WILLIAM F. SMITH
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

LORA M. GREEN
Administrative Patent Judge

) BOARD OF PATENT APPEALS AND INTERFERENCES

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